Clarke, Patrice A

From: Adams, Candace R.
Sent: Tuesday, June 25, 2002 3:57 PM
To: Tricker, Anthony
Cc: Roethig, Hans; Oey, Jan; Solana, Rick P.; Podraza, Ken F.; Kobal, Gerd; Walk, Roger A.; Carchman, Loreen; Dempsey, Ruth; Sanders, Edward; Reininghaus, Wolf; Patskan, George J.; Holt, Klaus von; Rustemeier, Klaus; Schepers, Georg; King, Valerie A.; Kinser, Robin D.
Subject: RE: re Draft protocol TES

Tony, Hans forwarded me your message expressing concern re: use of the topography devices. I think we all share a concern and recognize the need for obtaining unbiased estimates using measures that are nearly non intrusive. We also know that any research runs the risk of modifying behavior, whether it's collecting urine over a 24 hour period, participating in a confinement study, or asking adults to collect and return butts - - which is why we use elaborate experimental designs and sampling strategies in our clinical studies.

Nevertheless, you raise a valid concern. And, given the gravity of this concern, I checked three sources to lend substance to my reply rather than speculate whether using the topography devices would invalidate uptake measures. These include (1) a prominent tobacco researcher at VCU who has conducted studies using the topography device and published results in peer reviewed journals, (2) extant literature on smoking topography, and (3) internal PM documents.

(1) I talked with a prominent tobacco researcher at VCU who has used topography devices in several studies and asked him what his experiences have been. He does not believe use of a topography device significantly alters smoking behavior (although he added no one really knows whether it will or not). He concluded our discussing by saying his studies do not reveal that use of the topography device changed adult smokers' puffing profiles, thereby invalidating the biomarkers of exposure.

(2) There seems to be only one study where repeated measures were used to assess the impact of smoking with lip contact vs. a flowmeter holder. (See Hofer, I; Nil, R.; and Battig, K. Nicotine yield as determinant of smoke exposure indicators and puffing behavior. Pharmacology, Biochemistry, and Behavior. 40:139-149; 1991.) For this cross-sectional study, 18 male and 18 female subjects were recruited for each of four yield classes (Full flavor, medium, light and ultra light) for a total sample size of 144. Assignment to lip vs. holder smoking was randomized across subjects. In one condition (i.e., nonrestricted, natural smoking), smokers were instructed to smoke as they naturally do; in the second condition they were instructed to take 30 puffs from a half-cut cigarette (i.e., "forced smoking"), smokers Biomarkers included CO in expired air as well as nicotine and cotinine in plasma. Results from the natural smoking condition are summarized only. (Note: Standard deviations were not reported.)

Variable	Lip Smoking (Means)	Holder Smoking (Means)
Pre-to Post-smoking Boosts in:		
CO (ppm)	2.6	2.5
Nicotine (ng/ml)	9.1	8.5
Cotinine	0.0	0.2

Hofer et al. concluded that "(c)ontact condition hardly influenced the results. . . Smoking with a cigarette holder instead of normal lip contact changes some aspects of smoke absorption, puffing behavior, and subjective effects (i.e., strength, taste, satisfaction), but these changes are widely comparable over the whole range of nicotine yield. Yield specific holder effects emerged with respect to the number of puffs only. From lip to holder smoking, the number of puffs was increased more with low than high yield cigarettes, although these differences were less obvious for total puff duration. However, CO and nicotine boosts (i.e., the difference between post-smoking and pre-smoking measures) were independent of the contact condition" (Note: examples added).

Test-retest reliabilities for lip vs. holder smoking were high both for pre-smoking conditions (CO: .75; nicotine: .76, and cotinine :.83) and post-smoking conditions (CO: .80, nicotine: .78, and cotinine: .83).

(3) I reviewed old internal documents since, to my knowledge, research of this nature hasn't taken place since the 1970-80. This included reviews of studies by Barbro Goodman, Frank Ryan, and Bill Dunn but found nothing regarding smoking using a topography device. Hauserman (1972) who wrote about direct measures for investigating human smoking characteristics where a "cigarette is smoked in a special mouthpiece which is connected to instruments recording puff

number, interval between puffs, puff duration, puff volume and puff shape. He concludes "The big advantage of the direct measurement is the precision of the results . . . but are . . . almost certainly biased with respect to such important parameters as the interval between puffs and the butt length." However, Hausermann does not site specific research conducted at PM that allowed him to draw this conclusion.

Taken in the balance, we have compelling evidence to use the topography devices as proposed in the TES Protocol as the devices represent the only way to obtain precise measures of puff duration, puff peak and, puff volume -- parameters critical to our continued understanding of exposure. Nevertheless, we have opted to capitalize on Covance's learnings as a lead sight by introducing a small validation study into the protocol. That is, we will ask approximately 50 adult smokers to collect urine on two occasions. There would be a 24 hour collection using the topography device as well as a 24 hour collection not using the device. The 50 adult smokers will be randomly assigned to the two collection conditions such that half the sample will be randomly assigned to use of the topography device during the first 24 hour collection; the other half will be randomly assigned to use of the topography device during the second collection.

Respectfully,

Candace

-----Original Message-----
From: Roethig, Hans
Sent: Wednesday, June 19, 2002 8:57 AM
To: Adams, Candace R.
Subject: FW: re Draft protocol TES

FYI

-----Original Message-----
From: Tricker, Anthony
Sent: Tuesday, June 18, 2002 3:42 AM
To: Oey, Jan; Solana, Rick P.; Podraza, Ken F.; Kobal, Gerd; Walk, Roger A.; Carchman, Loreen; Dempsey, Ruth; Sanders, Edward; Reininghaus, Wolf; Patskan, George J.; Holt, Klaus von; Rustemeier, Klaus; Schepers, Georg; King, Valerie A.; Roethig, Hans
Cc: Kinser, Robin D.; Tricker, Anthony
Subject: RE: re Draft protocol TES

Re: Protocol No. PM-1337: A multi-center study to determine the exposure of adult U.S. smokers to cigarette smoke (Draft No. 2 dated 14th June 2002)

Dear Valerie,

I have a major technical issue and a rather long list of minor issues that need addressing.

A major technical issue:

I have a major concern that performing smoking topography measurements for every cigarette smoked will seriously affect the way the subjects smoke. Smoking every cigarette through a machine does not represent normal smoking behaviour, thus nearly all the biomarkers of exposure (with the exception of 4-aminobiphenyl hemoglobin adducts) will not provide a valid indication of smoke uptake) I would strongly recommend that serious thought be given to asking the subjects to smoke only two cigarettes to determine average smoking profiles and the two cigarettes should be smoked one on Visit 1 and one on Visit 2. How are the data to be evaluated if smoking profiles are determined for every cigarette? (please check this with Hans)

Minor issues:

Page 10, line 3 from bottom: correct to read "... so as to sample ..."

Page 11 (Recruitment): Will subject identification really be performed by television? (Also page 19).

Page 11, line 2 from bottom: Will cotinine be determined in blood and do we have a validated method? See also Table 1 (check with Robin).

Page 12 (Urine): nicotine metabolites should include *trans*-3'-hydroxycotinine-*O*-glucuronide in parentheses). This is a systematic mistake occurring through the text (see also Tables 1,2 and 5; page 47)

Page 12 (Urine): NNAL-glucuronides - I thought we were only determining NNAL-*O*-glucuronide although two glucuronides (NNAL-*O*-glucuronide and NNAL-*N*-glucuronide) have now been identified in human urine (see also Table 5; pages 47, 48) (check with Robin).

Page 12 (Sample banking): What is the logic for performing sample banking 1 year after sample collection? (check with Hans)

Page 12 (Questionnaires): Why are only non-smokers asked about ETS exposure - shouldn't both smokers and non-smokers be asked about ETS exposure. Also page 23.

Page 12 (Clinical Lab Tests): How can we be certain that subjects will fast for 6 hours? How critical is the fasting period for the clinical end points to be measured? (ask Hans)

Table 1: Some of the footnotes are incorrectly assigned in the table (e.g., g). This needs checking.

Page 16, 2nd bullet: change to read ".... gas/vapor phase ...."

Page 16, footnote: delete "and biomarkers of potential harm"

Table 2: 1-Hydroxypyrene is a biomarker for Pyrene in tobacco smoke. I suggest that the text is changed to "Pyrene (a surrogate marker for polycyclic aromatic hydrocarbons)"

Table 3: "Oxidant" should be changed to "Oxidants"

Table 3: Both von Willebrand factor antigen and microalbumin are indicators of endothelial cell damage (?) and not the health effects mentioned (check with Hans for appropriate wording).

Table 5: Is 5 mL urine sufficient to determine NNAL and NNAL-glucuronide (check with Robin).

Page 27 (Sample banking): how much material will be collected for sample banking - this needs to be given. Will the samples be coded in such a way as to be able to assign to different FTC tar bands? If not, what will the samples be compared to?

Page 28 (Smoking topography): see comment above

Page 29 (Analytical methodology and Table 6): The 'Pilot Study' did not validate the determination of nicotine + metabolites and NNK metabolites in urine by LCMSMS. Other methods were used. (check with Robin)

Table 6: Cigarette filters will not be analyzed by GC, rather the nicotine content of the filters will be analyzed by GC.

Page 43: Delete 3-aminobiphenyl from text, only 4-aminobiphenyl will be determined.

General comments:

No questionnaire/s supplied for review

No submission to IRB on genetic testing supplied for review. This is a very important part of the IRB submission.

Best regards,
Tony

-----Original Message-----
From: **Oey, Jan**
Sent: 14 juin 2002 23:48
To: Solana, Rick P.; Podraza, Ken F.; Kobal, Gerd; Walk, Roger A.; Carchman, Loreen; Dempsey, Ruth; Sanders, Edward; Reininghaus, Wolf; Patskan, George J.; Tricker, Anthony; Holt, Klaus von; Rustemeier, Klaus; Schepers, Georg
Cc: Roethig, Hans; King, Valerie A.
Subject: re Draft protocol TES

Dear All,

Please review the revised draft protocol and send your comments to Valerie by Jun 21.

Thank you for your help,
Jan

<< File: Protocol 8451-Draft 2 - 14 June 2002.doc >>